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| EXAMINER | |
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| CROUCH, DEBORAH | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | |

DATE MAILED: 07/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/808,382 | REUBINOFF ET AL. | |
| | Examiner | Art Unit | |
| | Deborah Crouch, Ph.D. | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 April 2004 and 06 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *39-46,51,56-58,60-68 and 86-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-46,51,56-58,60-68 and 86-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/3/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicants' Request for Continued Examination, filed April 5, 2004, is proper and has been entered.

Applicants' Amendments, filed April 5, 2004 and May 6, 2004 have been entered. Claims 39-46, 51, 56-58,60-68 and 86-94 are pending and under current examination.

This application has been transferred to Deborah Crouch, Ph.D., AU 1632.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 39-46 remain rejected under 35 U.S.C. 102(b) as being anticipated by Shamblott *et al.* [**PNAS**, 95:13726-13731, for reasons of record.

The claims are directed to methods of inducing somatic differentiation of stem cells *in vitro* into progenitor cells by obtaining undifferentiated human pluripotent ES cells and providing a controlled differentiating condition which is non-permissive for stem-cell renewal, does not kill cells or induces unidirectional differentiation toward extraembryonic lineages.

Claims 44 and 45 recite undifferentiated ES cells prepared by the method of by a specific method. Thus, the ES cells recited in these claims are product-by-process claims [see *supra*]. Note that with regard to claims 40 and 41, which discuss the expression of various undifferentiated embryonic stem cell markers, these markers are inherent properties of undifferentiated ES cells. That is, that, "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical

structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Shamblott teach the generation of pluripotent human ES cells from cultured human primordial germ cells. Gonadal ridges from post-fertilization human embryos were collected and the cells cultured. The cells were then analyzed by detection of AP activity and immunohistochemistry. See Materials and Methods. The cells were found to test positive for five immunological markers of ES cells [SSEA-1, SSEA-3, SSEA-4, TRA-1-60 and TRA-1-81], see Abstract. The immunohistochemical analysis of embryoid bodies revealed a wide variety of differentiated cell types, including derivatives of all three embryonic germ layers. See Abstract. Particularly, the immunohistochemical analysis of the embryoid bodies found ectodermal derivatives of cells suggestive of neuroepithelia and antineurofilament cells. See p. 13729, 2nd column, 1st full ¶. Shamblott teach that the cells are pluripotent stem cells that are positive for markers commonly used to identify pluripotent stem cells, have morphology similar to mouse ES and EG cells, maintain a normal and stable karyotype, and can be differentiated into a wide variety of cell types. See p. 13729, 2nd column, Discussion.

Applicant argues that the present claims are not anticipated by Shamblott because Shamblott does not teach a controlled differentiating condition, which is not permissive for stem cell renewal and does not kill cells or induce unidirectional differentiation towards extra-embryonic lineages as presently claims. Particularly, Applicants argue that Shamblott does not teach culturing the cells at either high density, for a long period of time, or in serum free media, as recited in claim 46. Further, Applicants argue that Shamblott do not teach culturing the cells on a fibroblast feeder layer that does not kill cells or induce unidirectional differentiation toward extra-embryonic lineages, and that Shamblott does not recognize that there are subsets of fibroblasts which would support controlled differentiation

of the ES cells. Applicant argues that the preparation, handling and testing of fibroblasts are important to the success of the claimed method. Applicant argues that Shamblott does not teach culturing the cells on semi-permeable membranes to create structures mimicking the post-implantation phase of human development, or culturing the cells in the presence of a chemical differentiation factor such as BMP-2. See Applicants arguments, pp. 10-11. Applicant argues that Shamblott identified neural cell types in EB's which were generated on with the addition of hrLIF to the cell culture. Applicant argues that the present specification teaches that LIF is not required for the induction of somatic differentiation of human ES cells. These arguments are not persuasive.

The specification does not provide a definition of "controlled differentiating condition" and thus the broadest reasonable interpretation of the claim has been given the term. The differentiation observed by Shamblott clearly is "controlled" in that the cells develop into all three embryonic germ layers. There is no stem cell renewal once the germ layers are formed and there is no taught unidirectional differentiation towards extraembryonic lineages, Thus, the characteristics of controlled differentiation as defined in the claim are met by Shamblott. With regards to claim 46, the conditions are in the alternative and to meet the claim only one of the alternatives needs to be met. Since there is no clear definition of "prolonged periods and at high density" in the specification, the culture conditions of Shamblott meet these particular characteristics. Further, the pluripotent ES cells formed EB's while cultured on STO feeder cells, making te feeder cells differentiation inducing fibroblasts without inducing extraembryonic lineages. Applicant's comments regarding the disclosure of LIF not being require for differentiation are directed to limitations not in the claim. Further, Shamblott is no required to teach anything regarding subsets of fibroblasts and their role in differentiation as such is not a limitation of the

claimed invention. For novelty and obviousness rejections, limitations are not read into the claims.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 51 is rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson et al (1998) Science 282, 1145-1147 in view of Brustle et al (1999) Science 285, pp. 754-756.

Thomson teaches the isolation of human pluripotent embryonic stem cells (page 146, col. 1, parag. 1 and 2). Thomson offers motivation in stating human ES cells can be differentiated into somatic cells to provide a potentially limited source of cells for drug discovery and transplantation therapies (pages 1146-1147, bridg. sent.). Thomson also states that the progresses made in the differentiation of mouse ES cells into somatic cells will be useful to direct the differentiation of human ES cells (page 1147, col. 1, lines 18-25). Brustle teaches methods of inducing differentiation of mouse ES cells to glial precursors, a somatic progenitor cell, by culturing mouse ES cells in the presence of FGF2 and PDGF-AA in DMEM/F12 media and on polyornithine coated dishes (page 754, col. 2, lines 1-7; and page 756, col. 1, ftnt 7, lines 14-27) The withdrawal of growth factors caused the progenitor/stem cells to differentiate into oligodendrocytes (page 754, col. 2, lines 13-15; and page 756, col. 1, ftnt 7, lines 30-31).

Thus, at the time of the instant invention, it would have been obvious to the ordinary artisan to culture human ES cells as taught by Thomson in DMEM/F12 media in the presence of FGF2 and PDGF-AA on polyornithine to form glial precursors and then in the absence of

the growth factors to induce the formation of astrocytes and oligodendrocytes as taught by Brustle to provide differentiated cells for drug discovery and/or transplantation therapies. The cited prior art provides sufficient suggestion, teaching and motivation to reach the claimed invention.

Claims 56-58 and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson et al (1998) Science 282, 1145-1147 in view of Brustle et al (1999) Science 285, pp. 754-756 and Stemple et al (1992) Cell 71, pp. 973-985.

Thomson teaches the isolation of human pluripotent embryonic stem cells (page 146, col. 1, parag. 1 and 2). Thomson offers motivation in stating human ES cells can be differentiated into somatic cells to provide a potentially limited source of cells for drug discovery and transplantation therapies (pages 1146-1147, bridg. sent.). Thomson also states that the progresses made in the differentiation of mouse ES cells into somatic cells will be useful to direct the differentiation of human ES cells (page 1147, col. 1, lines 18-25). Brustle teaches methods of inducing differentiation of mouse ES cells to glial precursors, astrocytes or oligodendrocytes, a somatic progenitor cell, by culturing mouse ES cells in the presence of FGF2, followed by culture in the presence of FGF2 and EGF presence of FGF2 and PDGF-AA in DMEM/F12 media and on polyornithine coated dishes (page 754, col. 2, lines 1-7; and page 756, col. 1, ftnt 7, lines 14-27). Stemple teaches that the differentiation of neural crest multipotent into neurons required growth on poly-D-lysine (page 982, figure 7). Stemple also teaches the growth of the neural stem cells in the presence of retinoic acid (page 983, col. 1, parag. 3, line 11-12). Laminin was known at the time of the instant invention to be an adhesive substrate for neural cell growth and differentiation.

Thus, at the time of the instant invention, it would have been obvious to the ordinary artisan to culture human ES cells as taught by Thomson in DMEM/F12 media in the presence of FGF2 and EGF on polyornithine to form neural precursors as taught by Brustle but

growing the precursors in media comprising retinoic acid and by growth on poly-D-lysine and laminin coated plates to induce neuronal growth as taught by Stemple for drug discovery and/or transplantation therapies. The cited prior art provides sufficient suggestion, teaching and motivation to reach the claimed invention. Applicant should note that the claims are not limited to producing neuronal cells.

Claims 60-63 and 87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson et al (1998) Science 282, 1145-1147 in view of Brustle et al al (1999) Science 285, pp. 754-756 and further in view of Stemple et al (1992) Cell 71, pp. 973-985 and Ben-Hur et al (1998) J. Neurosci. 18, pp. 5777-5788.

Thomson teaches the isolation of human pluripotent embryonic stem cells (page 146, col. 1, parag. 1 and 2). Thomson offers motivation in stating human ES cells can be differentiated into somatic cells to provide a potentially limited source of cells for drug discovery and transplantation therapies (pages 1146-1147, bridg. sent.). Thomson also states that the progresses made in the differentiation of mouse ES cells into somatic cells will be useful to direct the differentiation of human ES cells (page 1147, col. 1, lines 18-25). Brustle teaches methods of inducing differentiation of mouse ES cells to glial precursors, astrocytes or oligodendrocytes, a somatic progenitor cell, by culturing mouse ES cells in the presence of FGF2, followed by culture in the presence of FGF2 and EGF presence of FGF2 and PDGF-AA in DMEM/F12 media and on polyornithine coated dishes (page 754, col. 2, lines 1-7; and page 756, col. 1, ftnt 7, lines 14-27). Stemple teaches that neural crest multipotent cells cultured on poly-D-lysine and fibronectin coated plates differentiated into neurons, glia and oligodendrocytes (page 982, figure 7). Ben-Hur teaches the incubation of neural progenitor cells in the presence of EGF lead to the production primarily of astrocytes and oligodendrocytes (page 3784, figure 7). Ben-Hur also teaches that the culture of neural

stem cells in the presence of T3 also lead primarily to astrocytes and oligodendrocyte production.

Thus, at the time of the instant invention, it would have been obvious to the ordinary artisan to culture humàn ES cells as taught by Thomson in DMEM/F12 media in the presence of FGF2 and PDGF-AA on polyornithine to form glial precursors and then in the absence of the growth factors to form predominantly oligodendrocytes and astrocytes as taught by Brustle but growing the precursors on poly-D-lysine and fibronectin coated plates to enhance the presence of neurons in the differentiated cells and in the presence of EGF to enhance neuron differentiation followed by culture with EGF and T3 to produce a culture of neuronal cells, oligodendrocytes and glia cells for drug discovery and/or transplantation therapies. The cited prior art provides sufficient suggestion, teaching and motivation to reach the claimed invention. Applicant should note that the claims are not limited to producing glia cells.

Claims 64-68 and 88-94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson et al (1998) Science 282, 1145-1147 in view of Brustle et al (1999) Science 285, pp. 754-756.

Thomson teaches the isolation of human pluripotent embryonic stem cells from the inner cell mass of IVF human embryos, the culture of the ICM cells under conditions that promote proliferation of undifferentiated stem cells but where extraembryonic differentiation and cell death is not induced (page 146, col. 1, parag. 1 and 2). Thomson offers motivation in stating human ES cells can be differentiated into somatic cells to provide a potentially limited source of cells for drug discovery and transplantation therapies (pages 1146-1147, bridg. sent.). Thomson also states that the progresses made in the differentiation of mouse ES cells into somatic cells will be useful to direct the differentiation of human ES cells (page 1147, col. 1, lines 18-25). Brustle teaches methods of inducing differentiation of mouse ES

cells to glial precursors by culturing mouse EB's (clumps) in DMEM/F12 containing FGF2 and EGF to produce neural precursor cells (page 754, col. 1, parag. 2 to col. 2, lines 3; and page 756, col. 1, ftnt 7, lines 1-24). Ben-Hur teaches the culture of rat neural stem cell suspension in DMEM/F12 supplemented with B27, FGF2 and EGF to produce oligodendrocytes, such that NCAM-positive neurospheres formed (page 5782, col. 1, parag. 1, lines 1 to col. 2, lines 3).

Thus, at the time of the instant invention, it would have been obvious to the ordinary artisan to produce oligodendrocytes by culturing human ES cells produced as taught by Thomson in DMEM/F12 media in the presence of FGF2 and EGF to form glial precursors as taught by Brustle and to further culture the glia cells in the presence of B27, FGF2 and EGF in combinations to provide oligodendrocytes for drug discovery and/or transplantation therapies. The cited prior art provides sufficient suggestion, teaching and motivation to reach the claimed invention. The term "include" has been broadly interpreted to mean that the three growth factors B27, FGF2 and EGF are use in various combinations.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0408. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah Crouch

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July 26, 2004